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(54) Use of hydroxycarboxylic acids to enhance therapeutic effects of topical compositions for fungal infections and pigmented spots.

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CHEMICAL ABSTRACTS vol. 103, no.2, 15 July 1985, abstract no. 11494k, Columbus, Ohio, USA; & RO. A- 79 428 (28.2.1983)

(73) Proprietor: **Van Scott, Eugene J., Dr.**
3 Hidden Land
Abington
Pennsylvania 19001 (US)

Proprietor: **Yu, Ruey J., Dr.**
4 Lindenwold Avenue
Ambler
Pennsylvania 19002 (US)

(72) Inventor: **Van Scott, Eugene J., Dr.**
3 Hidden Land
Abington
Pennsylvania 19001 (US)
Inventor: **Yu, Ruey J., Dr.**
4 Lindenwold Avenue
Ambler
Pennsylvania 19002 (US)

(74) Representative: **Henkel, Feiler, Hänzel & Partner**
Möhlstrasse 37
D-81675 München (DE)

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Description

This invention relates generally to the use of a topical dermatologic agent together with hydroxyacid or related compound for enhancing therapeutic effects of cosmetic or pharmaceutical agent. As will be subsequently described in detail, we initially found that alpha hydroxy or keto acids and their derivatives were effective in the topical treatment of disease conditions such as dry skin, ichthyosis, eczema, palmar and plantar hyperkeratoses, dandruff, acne and warts.

We have now found that hydroxyacids or related compounds wherein incorporated into a therapeutic composition can substantially enhance topical effects of dermatologic agents.

In our prior U.S. Patent No. 3,879,537 entitled "Treatment of Ichthyosiform Dermatoses" we described and claimed the use of certain alpha hydroxy acids, alpha keto acids and related compounds for topical treatment of fish-scale like ichthyotic conditions in humans. In our U.S. Patent No. 3,920,835 entitled "Treatment of Disturbed Keratinization" we described and claimed the use of these certain alpha hydroxy acids, alpha keto acids and their derivatives for topical treatment of dandruff, acne, and palmar and plantar hyperkeratosis.

In our prior U.S. Patent No. 4,105,783 entitled "Treatment of Dry Skin: we described and claimed the use of alpha hydroxy acids, alpha keto acids and their derivatives for topical treatment of dry skin. In our recent U.S. Patent No. 4,246,261 entitled "Additives Enhancing Topical Corticosteroid Action" we described and claimed that alpha hydroxy acids, alpha keto acids and their derivatives, in small amounts could greatly enhance the therapeutic efficacy of corticosteroids in topical treatment of psoriasis, eczema, seborrheic dermatitis and other inflammatory skin conditions.

In our more recent U.S. Patent No. 4,363,815 entitled "Alpha Hydroxy acids, Alpha Keto acids and Their Use in Treating Skin Conditions" we described and claimed that alpha hydroxy acids and alpha keto acids related to or originating from amino acids, whether or not found in proteins, were effective in topical treatment of skin disorders associated with disturbed keratinization or inflammation. These skin disorders include dry skin, ichthyosis, palmar and plantar hyperkeratosis, dandruff, Darier's disease, lichen simplex chronicus, keratoses, acne, psoriasis, eczema, pruritus and possibly warts and herpes.

In our most recent U.S. Patent No. 4,518,789 entitled "Phenyl Alpha-Acyloxyacetamide Derivatives and Their Therapeutic Use" we described and claimed that phenyl alpha acyloxyacetamide derivatives in topical or systemic administration were useful and effective for pruritus, atopic dermatitis, eczema, psoriasis, acne, dry skin, dandruff, malodors of integumental areas, various aches, pains and discomforts of skin, joints and other body parts in humans and domestic animals.

Further, use of hydroxy acids is known from prior art documents as follows:

Chemical Abstracts Vol. 103, Nr. 2, 15 July 1985, Abstract No. 11494k describes a specific composition for treating dermatoses. This composition contains reductive diphenols, amino acids, phenolic acids, and plant extract, in addition to hydroxy acids and antimycotic substance. Enhancement of the therapeutic effect of this composition is not mentioned.

EP-A-0225005 (a document which has been published after the priority date of the present application) describes an adhesive preparation comprising a flexible support having laminated thereon a pressure-sensitive adhesive layer which contains i.a. an organic acid. This acid may be a carboxylic acid, e.g. citric acid, succinic acid, tartaric acid, and salicylic acid.

EP-A-0242967, also published after the priority date of the present application, describes a skin treatment composition containing minoxidil glucuronide and 2-hydroxypropionic acid as an activity enhancer. The purpose of this composition is the stimulation of hair growth or regrowth.

The intact skin of humans is a very effective barrier to many natural and synthetic substances. Cosmetic and pharmaceutical agents may be pharmacologically effective by systemic administration, but many of them are much less or totally ineffective on topical application to the skin. Topical effectiveness of a pharmaceutical agent depends on two major factors a) Percutaneous absorption and penetration b) Bioavailability of the penetrated pharmaceutical agent to the target site in the skin. To be therapeutically effective as a topical agent a pharmaceutical drug must penetrate the stratum corneum into the epidermal layers, distributed and bioavailable to the target sites for pharmacologic action. Many pharmacologic agents can readily penetrate the skin but they are not bioavailable to the target sites in the skin, therefore therapeutic effect is minimal and ineffective.

It has now been found that hydroxycarboxylic acids and related compounds can substantially enhance the therapeutic efficacy of dermatologic agents in topical treatment of fungal infections, and pigmented spots including pigmented age spots, melasma, and lentigines. Topical agents may include any chemical substances natural or synthetic, intended for the respective topical application to the skin or its appendages in human and animals.

The enhancing compounds of the instant invention are hydroxycarboxylic acids and related compounds. There are three groups of such hydroxyacids. The first is hydroxymonocarboxylic acids having the following chemical structure:

R_1 $(CR_2OH)_m(CH_2)_n$ COOH

wherein

R_1, R_2 = H, alkyl, aralkyl or aryl group of saturated or unsaturated, straight or branched chain or cyclic form, having 1 to 25 carbon atoms;

m = 1, 2, 3, 4, 5, 6, 7, 8 or 9

n = 0 or a numerical number up to 23

When n = 0 and m = 1 or more, the hydroxymonocarboxylic acid is also called aldonic acid. The name comes from a carbohydrate, aldose, which may be oxidized to aldonic acid by the oxidation of the aldehyde group in aldose to the carboyxlic group.

The hydroxymonocarboxylic acid may be present as a free acid, lactone, or salt form. The lactone form could be either inter or intramolecular lactone, however, most common ones are intramolecular lactones with a ring structure formed by elimination of one or more water molecules between a hydroxy group and the carboxylic group. Since the hydroxymonocarboxylic acids are organic in nature, they may form a salt or a complex with an inorganic or organic base such as ammonium hydroxide, sodium or potassium hydroxide, or triethanolamine.

The hydroxymonocarboxylic acid and its related compounds may also exist as stereoisomers such as D, L, and DL forms.

The typical alkyl, aralkyl and aryl groups for R_1 and R_2 include methyl, ethyl, propyl, isopropyl, benzyl and phenyl. The hydrogen atoms of the R_1 and R_2 and $(CH_2)_n$ may be substituted by a nonfunctional element such as F, Cl, Br, I, S or a radical such as a lower alkyl or alkoxy, saturated or unsaturated, having 1 to 9 carbon atoms. Representative hydroxymonocarboxylic acids are listed below:

1. 2-Hydroxyacetic acid (Glycolic acid)
R_1 = H, R_2 = H, m = 1, n = 0
2. 2-Hydroxypropanoic acid (Lactic acid)
R_1 = CH_3, R_2 = H, m = 1, n = 0
3. 2-Methyl 2-hydroxypropanoic acid (Methyllactic acid)
R_1 = CH_3, R_2 = CH_3, m = 1, n = 0
4. 2-Hydroxybutanoic acid
R_1 = C_2H_5, R_2 = H, m = 1, n = 0
5. Phenyl 2-hydroxyacetic acid (Mandelic acid)
R_1 = C_6H_5, R_2 = H, m = 1, n = 0
6. Phenyl 2-methyl 2-hydroxyacetic acid (Atrolactic acid)
R_1 = C_6H_5, R_2 = CH_3, m = 1, n = 0
7. 3-Phenyl 2-hydroxypropanoic acid (Phenyllactic acid)
R_1 = C_6H_5, R_2 = H, m = 1, n = 0
8. 2,3-Dihydroxypropanoic acid (Glyceric acid)
R_1 = H, R_2 = H, m = 2, n = 0
9. 2, 3, 4-Trihydroxybutanoic acid
R_1 = H, R_2 = H, m = 3, n = 0
10. 2, 3, 4, 5-Tetrahydroxypentanoic acid
R_1 = H, R_2 = H,m = 4, n = 0
11. 2, 3, 4, 5, 6-Pentahydroxyhenxanoic acid
R_1 = H, R_2 = H, m = 5, n = 0
12. 2-Hydroxydodecanoic acid (alpha hydroxylauric acid)
R_1 = $C_{10}H_{21}$, R_2 = H, m = 1, n = 0
13. 2, 3, 4, 5, 6, 7-Hexahydroxyheptanoic acid
R_1 = H, R_2 = H, m = 6, n = 0
14. Diphenyl 2-hydroxyacetic acid (benzilic acid)
R_1 = C_6H_5, R_2 = C_6H_5, m = 1, n = 0
15. 4-Hydroxymandelic acid
R_1 = $C_6H_4(OH)$, R_2 = H, m = 1, n = 0
16. 4-Chloromandelic acid
R_1 = $C_6H_4(Cl)$, R_2 = H, m = 1, n = 0
17. 3-Hydroxybutanoic acid
R_1 = CH_3, R_2 = H, m = 1, n = 1
18. 4-Hydroxybutanoic acid
R_1 = H, R_2 = H, m = a, n = 2
19. 2-Hydroxyhexanoic acid
R_1 = C_4H_9, R_2 = H, m = 1, n = 0
20. 5-Hydroxydodecanoic acid
R_1 = C_7H_{15}, R_2 = H, m = 1, n = 3
21. 12-Hydroxydodecanoic acid
R_1 = H, R_2 = H, m = 1, n = 10
22. 10-Hydroxydecanoic acid
R_1 = H, R_2 = H, m = 1, n = 8
23. 16-Hydroxyhexadecanoic acid
R_1 = H, R_2 = H, m = 1, n = 14
24. 2-Hydroxy-3-methylbutanoic acid
R_1 = C_3H_7, R_2 = H, m = 1, n = 0
25. 2-Hydroxy-4-methylpentanoic acid
R_1 = C_4H_9, R_2 = H, m = 1, n = 0
26. 3-Hydroxy-4-methoxymandelic acid
R_1 = C_6H_3 (OH) (OCH_3), R_2 = H, m = 1, n = 0
27. 4-Hydroxy-3-methoxymandelic acid
R_1 = C_6H_3 (OH) (OCH_3), R_2 = H, m = 1, n = 0
28. 2-Hydroxy-2-methylbutanoic acid
R_1 = C_2H_5, R_2 = CH_3, m = 1, n = 0
29. 3-(2-Hydroxyphenyl) lactic acid
R_1 = $C_6H_4(OH)$ CH_2, R_2 = H, m = 1, n = 0
30. 3-(4-Hydroxyphenyl) lactic acid
R_1 = $C_6H_4(OH)$ CH_2, R_2 = H, m = 1, n = 0
31. Hexahydromandelic acid
R_1 = C_6H_{11}, R_2 = H, m = 1, n = 0
32. 3-Hydroxy-3-methylpentanoic acid
R_1 = C_2H_5, R_2-CH_3, m = 1, n = 1
33. 4-Hydroxydecanoic acid
R_1 = C_6H_{13}, R_2 = H, m = 1, n = 2

34. 5-Hydroxydecanoic acid
$R_1 = C_5H_{11}$, $R_2 = H$, $m = 1$, $n = 3$
35. Aleuritic acid
$R_1 = C_6H_{12}(OH)$, $R_2 = H$, $m = 2$, $n = 7$

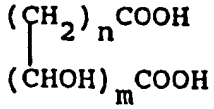
The linear lactic acid polymer is an intermolecular lactone formed by elimination of one water molecule between the hydroxy group of one molecule of lactic acid and the carboxylic group of a second molecule of lactic acid. The common linear lactic acid polymer may contain 3 lactic acid units.

Ribonic acid is one of the stereoisomers of 2, 3, 4, 5-tetrahydroxypentanoic acid, and the corresponding lactone is ribonolactone. Gluconic acid, galactonic acid, gulonic acid and mannonic acid are typical 2, 3, 4, 5, 6-pentahydroxyhexanoic acids and their corresponding lactones are gluconolactone, galactonolactone, gulonolactone and mannonolactone respectively. The related compounds of hydroxymonocarboxylic acids are ketomonocarboxylic acids which are formed from the former by a oxidation reaction or in vivo by a dehydrogenase enzyme. For example, 2-ketopropanoic acid (pyruvic acid) and 2-hydroxypropanoic acid (lactic acid) are converted to each other in vivo by the enzyme, lactate dehydrogenase. Although pure pyruvic acid (liquid form) can be kept in a refrigerator for an extended period of time a composition containing pyruvic acid for topical use is not very stable at a elevated temperature. Therefore, for practical purposes pyruvic acid esters are used instead.

The representative esters are methyl pyruvate, ethyl pyruvate, propyl pyruvate and isopropyl pyruvate. Other representative ketomonocarboxylic acids and their esters are phenyl pyruvic acid and its esters such as methyl phenyl pyruvate, ethyl phenyl pyruvate and propyl phenyl pyruvate; formyl formic acid (2-ketoacetic acid) and its esters such as methyl, ethyl and propyl formyl formate; benozyl formic acid and its esters such as methyl, ethyl and propyl benzoyl formate; 4-hydroxybenzoylformic acid and its esters; 4-hydroxyphenylpyruvic acid and its esters; 2-hydroxyphenylpyruvic acid and its esters.

Many hydroxy or ketomonocarboxylic acids are structurally related to amino acids either naturally occurring in proteins or not. For example alanine and pyruvic acid are interconverted to each other in vivo by an enzyme alanine dehydrogenease or alanine ketoglutarate transaminase. As mentioned earlier pyruvic acid and lactic acid are interconverted to each other in vivo by the enzyme lactate dehydrogenase. Therefore, alanine, pyruvic acid and lactic acid are chemically related in that the amino group of alanine may be converted to the keto group of pyruvic acid or the hydroxy group of lactic acid. The same relationships may apply to formyl formic acid and glycolic acid to glycine; hydroxypyruvic acid and glyceric acid to serine; phenyl pyruvic acid and phenyl lactic acid to phenylalanine; 2-keto- and 2-hydroxy-4 (methylthio) butanoic acids to methionine.

The second kind of hydroxyacid is hydroxydicarboxylic acid having the following chemical structure:



wherein
$m = 1, 2, 3, 4, 5, 6, 7, 8$ or 9
$n = 0$ or a numerical number up to 23

The hydroxydicarboxylic acid may also be present as a free acid, lactone or salt form. The lactone form could be either inter or intramolecular lactone. However, the common lactone is an intramolecular lactone with a ring structure formed by elimination of one or more water molecule between a hydroxy group and one of the carboxylic groups. Since the hydroxydicarboxylic acid is organic in nature, it may form a salt or a complex with an inorganic or organic base such as ammonium hydroxide. sodium or potassium hydroxide, or triethanolamine.

The hydroxydicarboxylic acid and its related compounds may also exist as stereoisomers such as D, L, DL and meso forms.

The hydrogen atom attached to the carbon atom may be substituted by a nonfunctional element such as F, Cl, Br, I, S or a radical such as a lower alkyl or alkoxy of saturated or unsaturated, having 1 to 9 carbon atoms.

When $n = 0$ and $m = 1$ or more, the hydroxydicarboxylic acid is also called aldaric acid. The name comes from the carbohydrate, and the common ones are saccharic acid and galactaric acid. Representative hydroxydicarboxylic acids are listed below:

1. 2-Hydroxypropanedioic acid (Tartronic acid)
$m = 1$, $n = 0$
2. 2-Hydroxybutanedioic acid (Malic acid)
$m = 1$, $n = 1$
3. Erythraric acid and Threaric acid (Tartaric acid)
$m = 2$, $n = 0$
4. Arabiraric acid, Ribaric acid, Xylaric acid and Lyxaric acid
$m = 3$, $n = 0$
5. Glucaric acid (saccharic acid), Galactaric acid (Mucic acid), Mannaric acid, Gularic acid, Allaric acid, Altraric acid, Idaric acid and Talaric acid
$m = 4$, $n = 0$

Commercially available saccharolactone (D-saccharic acid 1, 4-lactone) is an intramolecular lactone formed by elimination of one water molecule between the hydroxy group at position 4 and the carboxylic group at position 1.

The third type of hydroxyacid is a miscellaneous group of compounds which is not readily represented by the above generic structure of either the first type or the second type. Included in the third type of hydroxyacids are the following:

Hydroxycarboxylic acid of

$R(OH)_m(COOH)_n$

Wherein m,n = 1,2,3,4,5,6,7,8,or 9

R = H, alkyl, aralkyl or aryl group of saturated or unsaturated, straight or branched chain or cyclic form, having 1 to 25 carbon atoms.

citric acid, isocitric acid, citramalic acid, agaricic acid (n-hexadecylcitric acid), quinic acid, uronic acids including glucuronic acid, glucuronolactone, galacturonic acid, galacturonolactone, hydroxypyruvic acid, hydroxypyruvic acid phosphate, ascorbic acid, dihydroascorbic acid, dihydroxytartaric acid, 2-hydroxy-2-methylbutanoic acid, 1-hydroxy-1-cyclopropane carboxylic acid, 2-hydroxyhexanedial, 5-hydroxylysine, 3-hydroxy-2-aminopentanoic acid, tropic acid, 4-hydroxy-2, 2-diphenylbutanoic acid, 3-hydroxy-3-methylglutaric acid, and 4-hydroxy-3-pentenoic acid.

The third type of hydroxyacid may also be present as a free acid, lactone or salt form. The lactone form could be either an inter or intramolecular lactone, however, most common are intramolecular lactones with a ring structure. Commonly known glucuronolactone is a r-lactone i.e. 1,4-lactone of intramolecular type.

The hydroxyacid of the third type may also exist as stereoisomers such as D, L, DL and meso forms. The hydrogen atom attached to the carbon atom may be substituted by a nonfunctional element such as F, Cl, Br, I, S or a radical such as a lower alkyl or alkoxy of saturated or unsaturated, having 1 to 9 carbon atoms.

Any hydroxyacid and related compound of the above three kinds may be used as an additive in a combination composition to enhance the therapeutic efficacy of pharmaceutical agents.

The representative hydroxyacids are listed below:

citramalic acid, tropic acid, benzilic acid, ribonic acid and ribonolactone, gulonic acid and gulonolactone, 2,3,4-trihydroxybutanoic acid, 2,3,4,5-tetrahydroxypentanoic acid, 2,3,4,5,6-pentahydroxyhexanoic acid, 2-hydroxylauric acid, 2,3,4,5,6,7-hexahydroxyheptanoic acid, aleuritic acid, 4-hydroxymandelic acid, 4-chloromandelic acid, 2-hydroxy-3-methylbutanoic acid, 2-hydroxy-4-methylpentanoic acid, 3-hydroxy-3-methylbutanoic acid, 2-hydroxy-4-methylpentanoic acid, 3-hydroxy-4-methoxymandelic acid, 4-hydroxy-3-methoxymandelic acid, 3-(2-hydroxyphenyl) lactic acid, 3-(4-hydroxyphenyl) lactic acid, hexahydromandelic acid, 3-hydroxy-3-methylpentanoic acid, 1-hydroxy-1-cyclopropane carboxylic acid, 4-hydroxybutanoic acid, 2-hydroxyhexanoic acid, 5-hydroxylauric acid, 12-hydroxylauric acid, 10-hydroxydecanoic acid, 16-hydroxyhexadecanoic acid, 4-hydroxydecanoic acid, 5-hydroxydecanoic acid, and 4-hydroxy-2, 2-diphenylbutanoic acid.

Preparation of the Therapeutic Compositions

To prepare a therapeutic composition in solution form at least one of the aforementioned enhancing compounds of hydroxyacids and a dermatologic agent are dissolved in a solution which may consist of ethanol, water, propylene glycol, acetone or other pharmaceutically acceptable vehicles. The concentration of hydroxyacids may range from 0.01 to 99 percent by weight of the total composition. The concentration of the dermatologic agent ranges from 0.01 to 40 percent by weight of the total composition.

In the preparation of a therapeutic composition in cream or ointment form at least one of hydroxyacids and one of dermatologic agents are initially dissolved in a solvent such as water, ethanol, acetone, propylene glycol or polysorbate 80. the solution thus prepared is then mixed in a conventional manner with commonly available cream or ointment base such as hydrophilic ointment or petrolatum. The concentrations of hydroxyacids, cosmetic and pharmaceutical agents may range from 0.01 to 99 percent by weight of the total composition.

Therapeutic compositions of the instant invention may also be formulated in gel, lotion, shampoo, spray, stick or powder. A typical gel composition of the instant invention utilizes at least one of hydroxyacids and one of cosmetic or pharmaceutical agents dissolved in a mixture of ethanol, water and propylene glycol in a volume ratio of 40:40:20, respectively. A gelling agent such as hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose or ammoniated glycyrrhizinate is then added to the mixture with agitation. The preferred concentration of the gelling agent may range from 0.1 to 4 percent by weight of the total composition.

The following are illustrative examples of formulations and compositions according to this invention. Although the examples utilize only selected compounds and formulations, it should be understood that the following examples are illustrative and not limitative. Therefore, any of the aforementioned hydroxyacids and dermatologic agents

may be substituted according to the teachings of this invention in the following examples.

Example 1

A prophylactic and therapeutic composition in solution form for age spots may be prepared as follows.

Malic acid 1 gram, gluconolactone 19 grams and citric acid 0.5 gram are dissolved in a mixture of ethanol 30 ml, water 42 ml and glycerin 5 ml. Sodium bisulfite 0.5 g and hydroquinone 2 grams are added with stirring until a clear solution is obtained. The hydroxyacids, malic acid, gluconolactone and citric acid have been added a) as antioxidants to help stabilize the hydroquinone in the composition b) to enhance the penetration and the efficacy of hydroquinone c) to normalize the disturbed keratinization in age spot.

The composition thus formulated contains 2% hydroquinone, 1% malic acid, 19% gluconolactone, 0.5% citric acid, and has pH 3.3

Example 2

A therapeutic composition in solution form for age spots may be formulated as follows.

Alpha hydroxyisobutyric acid (Methyllactic acid) 20 grams and citric acid 2 grams are dissolved in a mixture of ethanol 49 ml, water 20 ml and propylene glycol 7 ml. Sodium bisulfite 0.5 g and hydroquinone 2 grams are added with stirring until a clear solution is obtained. The composition thus formulated contains 2% hydroquinone, 2% citric acid, 20% methyllactic acid, and has pH 3.6.

Example 3

A therapeutic composition containing clotrimazole and hydroxyacid for fungal infection may be formulated as follows.

Clotrimazole 1 gram and lactic acid 4 ml are dissolved in 4 ml of ethanol, and the solution thus obtained is mixed with 91 grams of hydrophilic ointment USP. The mixing is continued until a uniform consistency is obtained. The composition thus formulated contains 1% clotrimazole, 4% lactic acid, and has pH 3.2. The lactic acid has been added to enhance the penetration and the efficacy of clotrimazole for athlete's foot, and also to speed up healing and normalize the disturbed keratinization.

Example 4

A therapeutic composition containing griseofulvin and methyl pyruvate for fungal infection of nails may be formulated as follows.

Griseofulvin 1 gram and methyl pyruvate 2 ml are dissolved in a mixture of 2-pyrrolidone 20 ml. PEG-400 47 ml and ethanol 30 ml with stirring until the griseofulvin is completely dissolved. The composition thus formulated contains 1% griseofulvin, 2% methyl pyruvate, and has pH 4.4. The methyl pyruvate has been added to help griseofulvin dissolve into the solution, to enhance the penetration and the efficacy of griseofulvin, and to normalize the disturbed keratinization in nails.

Example 5

A therapeutic composition containing hydroquinone and lactic acid in solution form for age spots, melasmas, lentigines and other pigmented skin spots may be formulated as follows.

Lactic acid 10 ml, hydroquinone 4 grams and sodium metabisulfite 0.6 gram are dissolved in a mixture of ethanol 70 ml, water 10 ml and propylene glycol 6 ml with stirring until a clear solution is obtained. The composition thus formulated contains 4% hydroquinone, 10% lactic acid, and has pH 4.0. The lactic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions. The composition thus formulated is packaged in felt pens for controlled delivery to skin lesions.

Example 6

A therapeutic composition containing hydroquinone and glycolic acid in solution form for age-spots, melasmas, lentigines and other pigmented skin spots may be formulated as follows.

Glycolic acid 8 grams, hydroquinone 5 grams and sodium metabisulfite 0.5 gram are dissolved in a mixture of ethanol 70 ml, water 10 ml and propylene glycol 7 ml with stirring until a clear solution is obtained. The composition thus formulated contains 5% hydroquinone, 8% glycolic acid, and has pH 3.9. The glycolic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions. The composition thus prepared is packaged in felt pens for controlled delivery to skin lesions.

Example 7

A therapeutic composition containing hydroquinone and 2-methyl 2-hydroxypropanoic acid in solution form for age spots, keratoses, melasmas, lentigines and other pigmented skin spots may be formulated as follows.

2-Methyl 2-hydroxypropanoic acid 12 grams, hydroquinone 4 grams and sodium bisulfite 0.3

gram are dissolved in a mixture of ethanol 60 ml, water 20 ml and propylene glycol 4 ml with stirring until a clear solution is obtained. The composition thus formulated contains 4% hydroquinone, 12% 2-methyl 2-hydroxypropanoic acid, and has pH 4.0. The composition solution is packaged in felt pens for controlled delivery to skin lesions. The 2-methyl 2-hydroxypropanoic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions.

Comparative Example

A composition containing hydroquinone alone in solution form for age spots studies may be formulated as follows.

Hydroquinone 5 grams and sodium metal bisulfite 0.5 gram are dissolved in a mixture of ethanol 70 ml, water 15 ml and propylene glycol 10 ml with stirring until a clear solution is obtained. The composition thus prepared contains 5% hydroquinone and has pH 6.0. The composition solution is packaged in felt pens for comparative studies; with or without hydroxyacids on age spots.

TEST RESULTS

In order to determine whether addition of a hydroxyacid in the composition could enhance the therapeutic action of a dermatologic agent a total of more than 55 volunteers and patients having different skin disorders participated in these studies. Each participating subject was given two preparations; i.e. with or without the addition of a hydroxyacid in the therapeutic composition.

Topical applications were carried out either by bilateral or sequential comparison. In bilateral comparison the subject was instructed to apply one preparation on one side of the body and the other one on the other side of the body. For such cases where both sides were involved, the subject was instructed to apply two to three times daily one medication on one side of the body for a period of up to several months of time. The medication was discontinued whenever a total remission of the lesions occurred prior to the test period of up to several months.

For the scalp or face involvement the subject was instructed to apply two to three times daily one medication on one side of the scalp or the face and the other medication on the other side of the scalp or the face for a period of up to 12 weeks of time. For age spots, the medication was continued for up to 4 months of time.

Sequential administrations of medications were carried out whenever the bilateral comparison was difficult. 3. Age Spots and Pigmented Skin lesions.

Therapeutic compositions packaged in felt pens as described in Examples were provided to 14 patients for treatment of age spots, and other pigmented skin spots. Each participating patient received two felt pens; i.e. with or without the addition of hydroxyacid to the composition containing hydroquinone. The patients were instructed to apply topically one medication on one side of the body such as on the back of the left hand and the other medication on the other side of the body such as on the back of the right hand. Specific instructions were given to the patients that the medications were applied twice daily and discretely only to the skin lesions of age spots, melasmas, lentigines or other pigmented skin spots.

Within one to three weeks, improvement of age spots was clinically discernible. After one to three months substantial eradication of age spots occurred in all the patients tested. Complete eradication of age spots usually occurred within two to four months of topical administration in most cases. Therapeutic compositions containing higher concentrations of hydroxyacids (10 to 20%) and hydroquinone (3 to 5%) were judged to be more efficient in eradicating age spots within shorter periods of time. Without the addition of a hydroxyacid to the composition of hydroquinone, eradication of age spots did not occur within four months of time.

It was also found that while compositions containing hydroxyacids without hydroquinone were effective for eradication of certain disorders the compositions were not efficient in eradicating pigmented age spots, melasmas or lentigines within 4 months of time. In any case, with the addition of a hydroxyacid to the composition containing hydroquinone, pigmented age spots, melasmas, lentigines and other pigmented skin spots had been substantially eradicated.

Therapeutic compositions containing clotrimazole or griseofulvin with or without the addition of a hydroxyacid were provided to 6 patients having recurrent fungal infections of the foot; i.e. athlete's foot with or without toe nail involvement. Each participating patient received two medications with or without the addition of a hydroxyacid to the composition containing clotrimazole or griseofulvin. The patients were instructed to apply topically one medication on one side of the body such as left foot, and the other medication on the other side of the body such as right foot. Three time daily applications were continued for one to two weeks. When nail infections were involved the topical application was continued for up to 4 months using the compositions containing griseofulvin with or without the addition of a hydroxyacid.

The degree and rate of improvement on skin lesions were clinically evaluated, and comparison

was made one side of the body against the other. It was found that the skin lesions improved much faster with the compositions containing both the antifungal agent and the hydroxyacid. The presence of hydroxyacid appeared to enhance the efficacy of the antifungal agent, and also to eliminate the discomforts such as itching, tingling, burning and heat due to the fungal infection. Generally the infected skin healed within a week from topical application of the compositions containing an antifungal agent and a hydroxyacid. When toe nails were involved in the fungal infection the complete healing and regrowth of nails usually took several months on continued topical application of medications containing griseofulvin and a hydroxyacid.

The hydroxyacids and related compounds which may be useful as additives to enhance therapeutic effects of other dermatologic agents include 2-Hydroxyacetic acid; 2-hydroxypropanoic acid; 2-methyl 2-hydroxypropanoic acid; 2-hydroxybutanoic acid; phenyl 2-hydroxyacetic acid; phenyl 2-methyl 2-hydroxyacetic acid; 3-phenyl 2-hydroxyacetic acid; 2,3-dihyroxypropanoic acid; 2,3,4-trihydroxybutanoic acid; 2,3,4,5,6-pentahydroxyhexanoic acid; 2-hydroxydodecanoic acid; 2,3,4,5-tetrahydroxypentanoic acid; 2,3,4,5,6,7-hexahydroxyheptanoic acid; diphenyl 2-hydroxyacetic acid; 4-hydroxymandelic acid; 4-chloromandelic acid; 3-hydroxybutanoic acid; 4-hydroxybutanoic acid; 2-hydroxyhexanoic acid; 5-hydroxydodecanoic acid; 12-hydroxydodecanoic acid; 10-hydroxydecanoic acid; 16-hydroxyhexadecanoic acid; 2-hydroxy-3-methylbutanoic acid; 2-hydroxy-4-methylpentanoic acid; 3-hydroxy-4-methoxymandelic acid; 4-hydroxy-3-methoxymandelic acid; 2-hydroxy-2-methylbutanoic acid; 3-(2-hydroxphenyl) lactic acid; 3-(4-hydroxyphenyl) lactic acid; hexahydromandelic acid; 3-hydroxy-3-methylpentanoic acid; 4-hydroxydecanoic acid; 5-hydroxydecanoic acid; aleuritic acid.

2-Hydroxypropanedioic acid; 2-hydroxybutanedioic acid; erythraric acid; threaric acid; arabiraric acid; ribaric acid; xylaric acid; lyxaric acid; glucaric acid; galactaric acid; mannaric acid; gularic acid; allaric acid; altraric acid; idaric acid; talaric acid; 2-hydroxy-2-methylbutanedioic acid.

Citric acid, isocitric acid, agaricic acid, quinic acid, glucuronic acid, glucuronolactone, galacturonic acid, galacturonolactone, uronic acids, uronolactones, ascorbic acid, dihydroascorbic acid, dihydroxytartaric acid, tropic acid, ribonolactone, gluconolactone, galactonolactone, gulonolactone, mannonolactone, citramalic acid.

Pyruvic acid, hydroxypyruvic acid, hydroxypyruvic acid phosphate, their esters; methyl pyruvate, ethyl pyruvate, propyl pyruvate, isopropyl pyruvate; phenyl pyruvic acid, its esters; methyl phenyl pyruvate, ethyl phenyl pyruvate, propyl phenyl pyruvate; formyl formic acid; its esters; methyl formyl formate, ethyl formyl formate, propyl formyl formate; benzoyl formic acid, its esters; methyl benzoyl formate, ethyl benzoyl formate and propyl benzoyl formate; 4-hydroxybenzoyl formic acid, its esters; 4-hydroxyphenyl pyruvic acid, its esters; 2-hydroxyphenyl pyruvic acid and its esters.

Claims

1. Use of
   - a topical dermatologic agent together with
   - an enhancing effective amount of at least one compound selected from the group consisting of hydroxycarboxylic acids and ketocarboxylic acids and esters, lactones, or salt forms thereof, wherein the composition must not contain reductive diphenols together with a plant extract,

   for the preparation of a topical dermatologic therapeutic composition with enhanced therapeutic effect for use in the treatment of fungal infections, and pigmented spots including pigmented age spots, melasma, and lentigines.

2. Use of the composition of claim 1, wherein said agent is a member selected from the group consisted of:

   clotrimazole, candicidin; griseofulvin, hydroquinone and its monomethyl and benzyl ethers; ketoconazole, miconazole, nystatin, flucytosine, amphotericins and tolnaftate.

3. Use of the composition of claim 1 or 2 wherein said hydroxycarboxylic acid is

   hydroxymonocarboxylic acid having the following chemical structural formula:

   $R_1(CR_2OH)_m(CH_2)_nCOOH$

   wherein

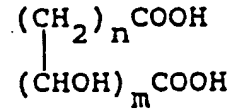
   R_1, R_2 = H, alkyl, aralkyl or aryl group of saturated or unsaturated, straight or branched chain or cyclic form, having 1 to 25 carbon atoms.
   m = 1,2,3,4,5,6,7,8 or 9
   n = 0 or a numerical number up to 23
   present as free acid, lactone or salt form, and as optically active or inactive isomer such as D, L, and DL forms; the hydrogen atom attached to the carbon atom may be substituted by a nonfunctional F, Cl, Br, I, or S atom or a lower alkyl or alkoxy saturated or unsaturated radical, having 1 to 9 carbon atoms.

4. Use of the composition of claim 3 wherein said hydroxymonocarboxylic acid is a member selected from the group consisted of 2-hydroxyacetic acid; 2-hydroxypropanoic acid; 2-methyl 2-hydroxypropanoic acid; 2-hydroxybutanoic acid; phenyl 2-hydroxyacetic acid; phenyl 2-methyl 2-hydroxyacetic acid; 3-phenyl 2-hydroxypropanoic acid; 2,3-dihydroxypropanoic acid; 2,3,4-trihydroxybutanoic acid; 2,3,4,5-tetrahydroxypentanoic acid; 2,3,4,5,6-pentahydroxyhexanoic acid; 2-hydroxydodecanoic acid; 2,3,4,5,6,7-hexahydroxyheptanoic acid; diphenyl 2-hydroxyacetic acid; 4-hydroxymandelic acid; 4-chloromandelic acid; 3-hydroxybutanoic acid; 4-hydroxybutanoic acid; 2-hydroxyhexanoic acid; 5-hydroxydodecanoic acid; 12-hydroxydodecanoic acid; 10-hydroxydecanoic acid; 16-hydroxyhexadecanoic acid; 2-hydroxy-3-methylbutanoic acid; 2-hydroxy-4-methylpentanoic acid; 3-hydroxy-4-methoxymandelic acid; 4-hydroxy-3-methoxymandelic acid; 2-hydroxy-2-methylbutanoic acid; 3-(2-hydroxyphenyl) lactic acid; 3-(4-hydroxyphenyl) lactic acid; hexahydromandelic acid; 3-hydroxy-3-methylpentanoic acid; 4-hydroxydecanoic acid; 5-hydroxydecanoic acid; aleuritic acid.

5. Use of the composition of claim 3 wherein said lactone is an intermolecular or intramolecular lactone including linear acid polymer, ribonolactone, gluconolactone, galactonolactone, gulonolactone and mannonolactone.

6. Use of the composition of claim 1 or 2 wherein said compound is a keto or hydroxyketomonocarboxylic acid selected from the group consisting of pyruvic acid, hydroxypyruvic acid, hydroxypyruvic acid phosphate, methyl pyruvate, ethyl pyruvate, propyl pyruvate, isopropyl pyruvate, phenyl pyruvic acid, methyl phenyl pyruvate, ethyl phenyl pyruvate, propyl phenyl pyruvate; formyl formic acid, methyl formyl formate, ethyl formyl formate, propyl formyl formate, benzoyl formic acid, methyl benzoyl formate, ethyl benzoyl formate, propyl benzoyl formate, 4-hydroxybenzoyl formic acid, 4-hydroxyphenyl pyruvic acid, and 2-hydroxyphenyl pyruvic acid.

7. Use of the composition of claim 1 or 2 wherein said compound is a hydroxydicarboxylic acid having the following chemical structural formula:



wherein
m = 1,2,3,4,5,6,7,8, or 9
n = 0 or a numerical number up to 23
present as free acid, lactone or salt form, and as optically active or inactive D, L, and meso isomer; hydrogen atom attached to the carbon atom may be substituted by a nonfunctional F, Cl, Br, I, or S atom or a lower alkyl or alkoxy saturated or unsaturated radical, having 1 to 9 carbon atoms.

8. Use of the composition of claim 7 wherein said hydroxydicarboxylic acid is a member selected from the group consisted of 2-hydroxypropanedioic acid; 2-hydroxybutanedioic acid; erythraric acid; threaric acid; arabiraric acid; ribaric acid; xylaric acid; lyxaric acid; glucaric acid; galactaric acid; mannaric acid; gularic acid; allaric acid; altraric acid; idaric acid; talaric acid; 2-hydroxy-2-methylbutanedioic acid.

9. Use of the composition of claim 7 wherein said lactone is an intermolecular or intramolecular lactone including saccharic acid, 1,4-lactone.

10. Use of the composition of claim 1 or 2 wherein said compound is a hydroxycarboxylic acid having the following formula:

$R(OH)_m(COOH)_n$

Wherein m,n = 1,2,3,4,5,6,7,8 or 9
R = alkyl, aralkyl or aryl group of saturated or unsaturated, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, present as free acid, lactone or salt form.

11. Use of the composition of claim 10 wherein said acid is a member selected from the group consisting of citric acid, isocitric acid, agaricic acid, quinic acid, citramalic acid, glucuronic acid, glucuronolactone, galacturonic acid, galacturonolactone, uronic acids, uronolactones, asorbic acid, dihydroascorbic acid, dihydroxytartaric acid, 1-hydroxy-1-cyclopropanecarboxylic acid, 5-hydroxylysine, 3-hydroxy-2-aminopentanoic acid; 4-hydroxy-3-pentenoicacid, 4-hydroxy-2, 2-diphenylbutanoic acid, and 3-hydroxy-3-methylglutaric acid and ester, lactone or salt forms thereof, and as an optically active or inactive D, L, DL or meso

isomer; the hydrogen atom attached to the carbon atom may be substituted by a nonfunctional F, Cl, Br, I or S atom or a lower alkyl or alkoxy saturated or unsaturated radical having 1 to 9 carbon atoms.

12. Use of the composition of claim 10 wherein the lactone is an inter or intramolecular lactone.

13. Use of the composition of claim 1 or 2 wherein said compound is selected from the group consisting of:

Citramalic acid, Diphenyl 2-hydroxyacetic acid (benzilic acid), 2-phenyl 3-hydroxypropanoic acid (tropic acid), aleuritic acid, ribonic acid, ribonoloactone, 2,3,4-trihydroxybutanoic acid, 2,3,4,5-tetrahydroxypentanoic acid, 2,3,4,5,6-pentahydroxyhexanoic acid, 2-hydroxylauric acid, 2,3,4,5,6,7-hexahydroxyheptanoic acid, 4-hydroxymandelic acid, 4-chloromandelic acid, 2-hydroxy-3-methylbutanoic acid, 2-hydroxy-4-methylpentanoic acid, 3-hydroxy-4-methoxymandelic acid, 4-hydroxy-3-methoxymandelic acid, 3-(3-hyroxphenyl) lactic acid, 3-(4-hydroxyphenyl) lactic acid, hexahydromandelic acid, 3-hydroxy-3-methylpentanoic acid, 1-hydroxy-1-cyclopropane carboxylic acid, 4-hydroxybutanoic acid, 2-hydroxyhexanoic acid, 5-hydroxylauric acid, 12-hydroxylauric acid, 10-hydroxydecanoic acid, 16-hydroxyhexadecanoic acid, 4-hydroxydecanoic acid, 5-hydroxydecanoic acid, and 4-hydroxy-2, 2-diphenylbutanoic acid as a free acid or salt form.

14. Use of the composition of any of claims 1 to 13 wherein the topical dermatologic agent is selected from the group consisting of hydroquinone and hydroquinone monoether including menomethyl and monobenzyl ether.

15. Use of the composition of claim 14 wherein said hydroxycarboxylic acids and related ketocarboxylic acid and ester, lactone or salt forms thereof include glycolic acid, benzilic acid, tropic acid, lactic acid, malic acid, citric acid, isocitric acid, citramalic acid, tartronic acid, tartaric acid, gluconic acid, galactonic acid, alpha hydroxyisobutyric acid, phenyllactic acid, mandelic acid, atrolactic acid, gluconolactone, galactonolactone, ribonic acid, ribonolactone, pantoic acid, pantolactone, pantothenic acid, alpha hydroxybutyric acid, Beta hydroxybutyric acid, quinic acid, pyruvic acid, phenyl pyruvic acid, methyl pyruvate, ethyl pyruvate, ascorbic acid, benzoyl formic acid, methyl benzoyl formate, and ethyl benzoyl formate.

16. Use of the composition of any of claims 1 to 13 wherein the topical dermatologic agent is an antifungal agent.

17. Use of the composition of any of claims 1 to 4 wherein said hydroxycarboxylic acid is glycolic acid.

18. Use of the composition of any of claims 1 to 4 wherein said hydroxycarboxylic acid is lactic acid.

19. Use of the composition of claim 10 wherein said hydroxycarboxylic acid is citric acid.

20. Use of the composition of claim 13 wherein said hydroxycarboxylic acid is gluconolactone.

21. Use of the composition of claim 7 wherein said hydroxycarboxylic acid is tartaric acid.

Patentansprüche

1. Verwendung eines topischen dermatologischen Mittels zusammen mit einer verstärkend wirkenden Menge mindestens einer Verbindung, ausgewählt aus der Gruppe Hydroxycarbonsäuren und Ketocarbonsäuren und deren Ester, Lactone oder Salze, wobei die Zubereitung keine reduzierenden Biphenole zusammen mit einem Pflanzenextrakt enthalten darf, zur Herstellung einer topischen dermatologischen therapeutischen Zubereitung mit verstärkter therapeutischer Wirkung zur Verwendung bei der Behandlung von Pilzinfektionen und Pigmentflecken, einschließlich pigmentierter Altersflecken, Melasmen und Linsenflecken.

2. Verwendung der Zubereitung nach Anspruch 1, wobei das Mittel aus einer Komponente aus der Gruppe Clotrimazol, Candicidin, Griseofulvin, Hydrochinon und dessen Monomethyl- und Benzylether, Ketoconazol, Miconazol, Nystatin, Flucytosin, Amphotericinen und Tolnaftat ausgewählt ist.

3. Verwendung der Zubereitung nach Anspruch 1 oder 2, wobei die Hydroxycarbonsäure aus einer Hydroxymonocarbonsäure der folgenden chemischen Strukturformel:

$R_1(CR_2OH)_m(CH_2)_nCOOH$

worin bedeuten:

R1 und R_2 H oder eine gesättigte oder ungesättigte, gerad- oder verzweigtkettige oder cyclische Alkyl-, Aralkyl- oder Arylgruppe mit 1 bis 25 Kohlenstoffatom(en);

m 1, 2, 3, 4, 5, 6, 7, 8 oder 9 und

n 0 oder eine numerische Zahl von bis zu 23,

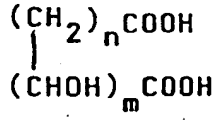
in Form der freien Säure, des Lactons oder in Salzform oder aus einem optisch aktiven oder inaktiven Isomer, wie den D-, L- und DL-Formen, besteht, wobei das am Kohlenstoffatom hängende Wasserstoffatom durch ein nicht funktionelles F-, Cl-, Br-, I- oder S-Atom oder einen gesättigten oder ungesättigten Niedrigalkyl- oder Alkoxyrest mit 1 bis 9 Kohlenstoffatom(en) ersetzt sein kann.

4. Verwendung der Zubereitung nach Anspruch 3, wobei die Hydroxymonocarbonsäure aus einer Komponente, ausgewählt aus der Gruppe 2-Hydroxyessigsäure, 2-Hydroxypropansäure, 2-Methyl-2-hydroxypropansäure, 2-Hydroxybutansäure, Phenyl-2-hydroxyessigsäure, Phenyl-2-methyl-2-hydroxyessigsäure, 3-Phenyl-2-hydroxypropansäure, 2,3-Dihydroxypropansäure, 2,3,4-Trihydroxybutansäure, 2,3,4,5-Tetrahydroxypentansäure, 2,3,4,5,6-Pentahydroxyhexansäure, 2-Hydroxydodecansäure, 2,3,4,5,6,7-Hexahydroxyheptansäure, Diphenyl-2-hydroxyessigsäure, 4-Hydroxymandelsäure, 4-Chlormandelsäure, 3-Hydroxybutansäure, 4-Hydroxybutansäure, 2-Hydroxyhexansäure, 5-Hydroxydodecansäure, 12-Hydroxydodecansäure, 10-Hydroxydecansäure, 16-Hydroxyhexadecansäure, 2-Hydroxy-3-methylbutansäure, 2-Hydroxy-4-methylpentansäure, 3-Hydroxy-4-methoxymandelsäure, 4-Hydroxy-3-methoxymandelsäure, 2-Hydroxy-2-methylbutansäure, 3-(2-Hydroxyphenyl)milchsäure, 3-(4-Hydroxyphenyl)milchsäure, Hexahydromandelsäure, 3-Hydroxy-3-methylpentansäure, 4-Hydroxydecansäure, 5-Hydroxydecansäure und Aleuritinsäure, besteht.

5. Verwendung der Zubereitung nach Anspruch 3, wobei das Lacton aus einem intermolekularen oder intramolekularen Lacton, einschließlich einem linearen Säurepolymer, Ribonolacton, Gluconolacton, Galactonolacton, Gulonolacton und Mannonolacton, besteht.

6. Verwendung der Zubereitung nach Anspruch 1 oder 2, wobei die Verbindung aus einer Keto- oder Hydroxyketomonocarbonsäure, ausgewählt aus der Gruppe Brenztraubensäure, Hydroxybrenztraubensäure, Hydroxybrenztraubensäurephosphat, Methylpyruvat, Ethylpyruvat, Propylpyruvat, Isopropylpyruvat, Phenylbrenztraubensäure, Methylphenylpyruvat, Ethylphenylpyruvat, Propylphenylpyruvat, Formylameisensäure, Methylformylformiat, Ethylformylformiat, Propylformylformiat, Benzoylameisensäure, Methylbenzoylformiat, Ethylbenzoylformiat, Propylbenzoylformiat, 4-Hydroxybenzoylameisensäure, 4-Hydroxyphenylbrenztraubensäure und 2-Hydroxyphenylbrenztraubensäure, besteht.

7. Verwendung der Zubereitung nach Anspruch 1 oder 2, wobei die Verbindung aus einer Hydroxydicarbonsäure der folgenden chemischen Strukturformel:



worin bedeuten:

m 1, 2, 3, 4, 5, 6, 7, 8 oder 9 und

n 0 oder eine numerische Zahl von bis zu 23,

in Form der freien Säure, eines Lactons oder in Salzform oder einem optisch aktiven oder inaktiven D-, L- oder meso-Isomeren besteht, wobei das an dem Kohlenstoffatom hängende Wasserstoffatom durch ein nicht funktionelles F-, Cl-, Br-, I- oder S-Atom oder einen gesättigten oder Ungesättigten Niedrigalkyl- oder Alkoxyrest mit 1 bis 9 Kohlenstoffatom(en) ersetzt sein kann.

8. Verwendung der Zubereitung nach Anspruch 7, wobei die Hydroxydicarbonsäure aus einer Komponente, ausgewählt aus der Gruppe 2-Hydroxypropandisäure, 2-Hydroxybutandisäure, Erythrarinsäure, Threarinsäure, Arabirarinsäure, Ribarinsäure, Xylarinsäure, Lyxarinsäure, Glucarinsäure, Galactarinsäure, Mannarinsäure, Gularinsäure, Allarinsäure, Altrarinsäure, Idarinsäure, Talarinsäure und 2-Hydroxy-2-methylbutansäure, besteht.

9. Verwendung der Zubereitung nach Anspruch 7, wobei das Lacton aus einem intermolekularen oder intramolekularen Lacton, einschließlich Zuckersäure und 1,4-Lacton, besteht.

10. Verwendung der Zubereitung nach Anspruch 1 oder 2, wobei es sich bei der Verbindung um eine Hydroxycarbonsäure der folgenden Formel:

$R(OH)_m(COOH)_n$

worin bedeuten:

m und n 1, 2, 3, 4, 5, 6, 7, 8 oder 9 und

R eine gesättigte oder ungesättigte, gerad- oder verzweigtkettige oder cyclische Alkyl-,

Aralkyl- oder Arylgruppe mit 1 bis 25 Kohlenstoffatom(en), in Form der freien Säure, des Lactons oder in Salzform handelt.

11. Verwendung der Zubereitung nach Anspruch 10, wobei die Säure aus einer Komponente, ausgewählt aus der Gruppe Zitronensäure, Isozitronensäure, Agaricinsäure, Chinasäure, Citramalinsäure, Glucuronsäure, Glucuronolacton, Galacturonsäure, Galacturonolacton, Uronsäuren, Uronolactone, Ascorbinsäure, Dihydroascorbinsäure, Dihydroxyweinsäure, 1-Hydroxy-1-cyclopropancarbonsäure, 5-Hydroxylysin, 3-Hydroxy-2-aminopentansäure, 4-Hydroxy-3-pentensäure, 4-Hydroxy-2,2-diphenylbutansäure und 3-Hydroxy-3-methylglutarsäure und deren Ester, Lactone oder Salze sowie deren optisch aktive oder inaktive D-, L-, DL- oder meso-Isomeren, besteht, wobei das am Kohlenstoffatom hängende Wasserstoffatom durch ein nicht funktionelles F-, Cl-, Br-, I- oder S-Atom oder einen gesättigten oder ungesättigten Niedrigalkyl- oder Alkoxyrest mit 1 bis 9 Kohlenstoffatom(en) ersetzt sein kann.

12. Verwendung der Zubereitung nach Anspruch 10, wobei das Lacton aus einem inter- oder intramolekularen Lacton besteht.

13. Verwendung der Zubereitung nach Anspruch 1 oder 2, wobei die Verbindung aus der Gruppe Citramalinsäure, Diphenyl-2-hydroxyessigsäure (Benzilsäure), 2-Phenyl-3-hydroxypropansäure (Tropasäure), Aleuritinsäure, Ribonsäure, Ribonolacton, 2,3,4-Trihydroxybutansäure, 2,3,4,5-Tetrahydroxypentansäure, 2,3,4,5,6-Pentahydroxyhexansäure, 2-Hydroxylaurinsäure, 2,3,4,5,6,7-Hexahydroxyheptansäure, 4-Hydroxymandelsäure, 4-Chlormandelsäure, 2-Hydroxy-3-methylbutansäure, 2-Hydroxy-4-methylpentansäure, 3-Hydroxy-4-methoxymandelsäure, 4-Hydroxy-3-methoxymandelsäure, 3-(3-Hydroxyphenyl)milchsäure, 3-(4-Hydroxyphenyl)milchsäure, Hexahydromandelsäure, 3-Hydroxy-3-methylpentansäure, 1-Hydroxy-1-cyclopropancarbonsäure, 4-Hydroxybutansäure, 2-Hydroxyhexansäure, 5-Hydroxylaurinsäure, 12-Hydroxylaurinsäure, 10-Hydroxydecansäure, 16-Hydroxyhexadecansäure, 4-Hydroxydecansäure, 5-Hydroxydecansäure und 4-Hydroxy-2,2-diphenylbutansäure in Form der freien Säure oder als Salz ausgewählt ist.

14. Verwendung der Zubereitung nach einem der Ansprüche 1 bis 13, wobei das topische dermatologische Mittel aus der Gruppe Hydrochinon und Hydrochinonmonoether, einschließlich dem Monomethyl- und Monobenzylether, ausgewählt ist.

15. Verwendung der Zubereitung nach Anspruch 14, wobei die Hydroxycarbonsäuren und verwandten Ketocarbonsäuren und deren Ester, Lactone oder Salze Glycolsäure, Benzilsäure, Tropasäure, Milchsäure, Äpfelsäure, Zitronensäure, Isozitronensäure, Citramalinsäure, Tartronsäure, Weinsäure, Gluconsäure, Galactonsäure, α-Hydroxyisobuttersäure, Phenylmilchsäure, Mandelsäure, Atromilchsäure, Gluconolacton, Galactonolacton, Ribonsäure, Ribonolacton, Pantonsäure, Pantolacton, Pantothensäure, α-Hydroxybuttersäure, β-Hydroxybuttersäure, Chinasäure, Brenztraubensäure, Phenylbrenztraubensäure, Methylpyruvat, Ethylpyruvat, Ascorbinsäure, Benzoylameisensäure, Methylbenzoylformiat und Ethylbenzoylformiat umfassen.

16. Verwendung der Zubereitung nach einem der Ansprüche 1 bis 13, wobei das topische dermatologische Mittel aus einem Antipilzmittel besteht.

17. Verwendung der Zubereitung nach einem der Ansprüche 1 bis 4, wobei die Hydroxycarbonsäure aus Glycolsäure besteht.

18. Verwendung der Zubereitung nach einem der Ansprüche 1 bis 4, wobei die Hydroxycarbonsäure aus Milchsäure besteht.

19. Verwendung der Zubereitung nach Anspruch 10, wobei die Hydroxycarbonsäure aus Zitronensäure besteht.

20. Verwendung der Zubereitung nach Anspruch 13, wobei die Hydroxycarbonsäure aus Gluconolacton besteht.

21. Verwendung der Zubereitung nach Anspruch 7, wobei die Hydroxycarbonsäure aus Weinsäure besteht.

Revendications

1. Utilisation de
- un agent dermatologique topique, conjointement avec
- une quantité efficace d'amélioration d'au moins un composé sélectionné dans le groupe constitué par les acides hydroxycarboxyliques et les acides cétocarboxyliques, et leurs esters,leurs lactones ou leurs formes salines, la composition ne devant pas contenir de diphénols réducteurs conjointement avec un extrait de

plante,

pour la préparation d'une composition thérapeutique dermatologique topique présentant un effet thérapeutique amélioré pour l'utilisation dans le traitement des infections mycotiques et les taches pigmentées, notamment les taches pigmentées du vieillissement, les mélanoses et les lentigines.

2. Utilisation de la composition de la revendication 1, dans laquelle ledit agent est un élément sélectionné dans le groupe constitué par :

le clotrimazole, la candicidine ; la griséofulvine, l'hydroquinone et ses éthers monométhyle et benzyle ; le cétoconazole, le miconazole, la nystatine, la flacytosine, les amphotéricines et le tolnaphtate.

3. Utilisation de la composition de la revendication 1 ou 2, dans laquelle ledit acide hydroxycarboxylique est

de l'acide hydroxymonocarboxylique présentant la formule structurelle chimique suivante :

$R_1(CR_2OH)_m(CH_2)_n\ COOH$

dans laquelle

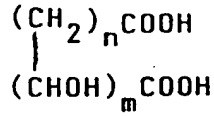
R_1, R_2 = H , groupe alkyle, aralkyle ou aryle de forme saturée ou non saturée, ou à chaîne linéaire ou ramifiée ou cyclique, présentant 1 à 25 atomes de carbone.
m = 1,2,3,4,5,6,7,8 ou 9
n = 0 ou un nombre numérique jusqu'à 23,
présent sous la forme d'un acide libre, de lactone ou de sel, et comme isomère optiquement actif ou inactif tel que les formes D, L, et DL ; l'atome d'hydrogène attaché à l'atome de carbone peut être remplacé par un atome non fonctionnel F, Cl, Br, I ou S ou un radical inférieur alkyle ou alkoxy saturé ou non saturé, présentant 1 à 9 atomes de carbone.

4. Utilisation de la composition de la revendication 3, dans laquelle ledit acide hydroxymonocarboxylique est un élément sélectionné dans le groupe constitué par
l'acide 2-hydroxyacétique ; l'acide 2-hydroxypropanoïque; l'acide 2-méthyle 2-hydroxypropanoïque; l'acide 2-hydroxybutanoïque ; l'acide phényle 2-hydroxyacétique ; l'acide phényle 2-méthyle 2-hydroxyacétique ; l'acide 3-phényle-2-hydroxypropanoïque ; l'acide 2,3-dihydroxypropanoïque; l'acide 2,3,4-trihydroxybutanoïque; l'acide 2,3,4,5-tétrahydroxypentanoïque; l'acide 2,3,4,5,6-pentahydroxyhexanoïque; l'acide 2-hydroxydodécanoïque; l'acide 2,3,4,5,6,7-hexahydroxyheptanoïque; l'acide diphényle 2-hydroxyacétique ; l'acide 4-hydroxymandélique; l'acide 4-chloromandélique; l'acide 3-hydroxybutanoïque; l'acide 4-hydroxybutanoïque; l'acide 2-hydroxyhexanoïque ; l'acide 5-hydroxydodécanoïque; l'acide 12-hydroxydodécanoïque; l'acide 10-hydroxydécanoïque ; l'acide 16-hydroxyhexadécanoïque; l'acide 2-hydroxy-3-méthylbutanoïque; l'acide 2-hydro-4-méthylpentanoïque; l'acide 3-hydroxy-4-méthoxymandelique; l'acide 4-hydroxy-3-méthoxymandélique; l'acide 2-hydroxy-2-méthylbutanoïque; l'acide 3-(2-hydroxyphényle) lactique ; l'acide 3-(4-hydroxyphényle) lactique; l'acide hexahydromandélique; l'acide 3-hydroxy-3-méthylpentanoïque; l'acide 4-hydroxydécanoïque, l'acide 5-hydroxydecanoïque; l'acide aleuritique.

5. Utilisation de la composition de la revendication 3, dans laquelle ladite lactone est une lactone intermoléculaire ou intramoléculaire, notamment un polymère acide linéaire, la ribonolactone, la gluconolactone , la galactonolactone, la gulonolactone et la mannonolactone.

6. Utilisation de la composition de la revendication 1 ou 2, dans laquelle ledit composé est un acide céto ou hydroxycétomonocarboxylique sélectionné dans le groupe constitué par l'acide pyruvique, l'acide hydroxypyruvique, le phosphate d'acide hydroxypyruvique, le pyruvate de méthyle, le pyruvate d'éthyle, le pyruvate de propyle, le pyruvate d'isopropyle, l'acide phényle pyruvique, le pyruvate de méthyle phényle, le pyruvate d'éthyle phényle, le pyruvate de propyle phényle ; l'acide formyle formique, le formate de méthyle formyle, le formate d'éthyle formyle, le formate de propyle formyle, l'acide benzoyle formique, le formate de méthyle benzoyle, le formate d'éthyle benzoyle, le formate de propyle benzoyle, l'acide formique 4-hydroxybenzoyle, l'acide pyruvique 4-hydroxyphényle et l'acide pyruvique 2-hydroxyphényle.

7. Utilisation de la composition de la revendication 1 ou 2, dans laquelle ledit composé est un acide hydroxydicarboxylique présentant la formule structurelle chimique suivante :



dans laquelle

m = 1,2,3,4,5,6,7,8, ou 9
n = 0 ou un nombre numérique jusqu'à 23,
présent comme forme acide libre, lactone ou sel, et comme isomère optiquement actif ou inactif D,L, et méso ; l'atome d'hydrogène attaché à l'atome de carbone peut être remplacé par un atome non fonctionnel F, Cl, Br, I ou S ou un radical inférieur alkyle ou alkoxy saturé ou non saturé, présentant 1 à 9 atomes de carbone.

8. Utilisation de la composition de la revendication 7, dans laquelle ledit acide hydroxydicarboxylique est un élément choisi dans le groupe constitué par
l'acide 2-hydroxypropanedioïque; l'acide 2-hydroxybutanedioïque ; l'acide érythrarique; l'acide thréarique; l'acide arabirarique; l'acide ribarique; l'acide xylarique; l'acide lyxarique ; l'acide glucarique; l'acide galactarique, l'acide mannarique; l'acide gularique; l'acide allarique ; l'acide altrarique; l'acide idarique; l'acide talarique; l'acide 2-hydroxy-2-méthylbutanedioïque.

9. Utilisation de la composition de la revendication 7, dans laquelle ladite lactone est unelactone intermoléculaire ou intramoléculaire, notamment l'acide saccharique, 1,4-lactone.

10. Utilisation de la composition de la revendication 1 ou 2, dans laquelle ledit composé est un acide hydroxycarboxylique présentant la formule suivante :

$R\ (OH)_m\ (COOH)_n$

dans laquelle m,n = 1,2,3,4,5,6,7,8 ou 9
R = groupe alkyle, aralkyle ou aryle de forme saturée ou non saturée, à chaîne linéaire ou ramifiée ou cyclique, présentant 1 à 25 atomes de carbone,
présent comme forme acide libre, lactone ou sel.

11. Utilisation de la composition de la revendication 10, dans laquelle ledit acide est un élément sélectionné dans le groupe constitué par l'acide citrique, l'acide isocitrique, l'acide agaricique, l'acide quinique, l'acide citramalique, l'acide glucuronique, la glucuronolactone, l'acide galacturonique, la galacturonolactone, les acides uroniques, les uronolactones, l'acide ascorbique l'acide dihydroascorbique, l'acide dihydroxytartarique, l'acide 1-hydroxy-1-cyclopropanecarboxylïque, la 5-hydroxylysine, l'acide 3-hydroxy-2-aminopentanoïque, l'acide 4-hydroxy-3-penténoïque, l'acide 4-hydroxy-2, 2-diphénylbutanoïque, et l'acide 3-hydroxy-3-méthylglutarique , et leurs formes ester, lactone ou sel, et comme isomère optiquement actif ou inactif D,L, DL ou méso ; l'atome d'hydrogène attaché à l'atome de carbone peut être remplacé par un atome non fonctionnel F, Cl, Br, I ou 5 ou un radical inférieur alkyle ou alkoxy saturé ou non saturé présentant 1 à 9 atomes de carbone.

12. Utilisation de la composition de la revendication 10, dans laquelle la lactone est unelactone inter ou intramoléculaire.

13. Utilisation de la composition de la revendication 1 ou 2, dans lequelle ledit composé est sélectionné dans le groupe constitué par :
l'acide citramalique, l'acide diphényle 2-hydroxyacétique (acide benzilique), l'acide 2-phényle 3-hydroxypropanoïque (acide tropique), l'acide aleuritique, l'acide ribonique, la ribonoloactone, l'acide 2,3,4-trihydroxybutanoïque, l'acide 2,3,4,5-tétrahydroxypentanoïque, l'acide 2,3,4,5,6-pentahydroxyhexanoïque, l'acide 2-hydroxylaurique, l'acide 2,3,4,5,6,7- hexahydroxyheptanoïque, l'acide 4-hydroxymandélique, l'acide 4-chloromandélique, l'acide 2-hydroxy-3-méthylbutanoïque, l'acide 2-hydroxy-4-méthylpentanoïque, l'acide 3-hydroxy-4-méthoxymandélique, l'acide 4-hydroxy-3-méthoxymandélique, l'acide 3-(3-hydroxyphényle)lactique, l'acide 3-(4-hydroxyphényle)-lactique, l'acide hexahydromandélique, l'acide 3-hydroxy-3-méthylpentanoïque, l'acide 1-hydroxy-1-cyclopropane carboxylique, l'acide 4-hydroxybutanoïque, l'acide 2-hydroxyhexanoïque, l'acide 5-hydroxylaurique, l'acide 12-hydroxylaurique, l'acide 10-hydroxydécanoïque, l'acide 16-hydroxyhexadécanoïque, l'acide 4-hydroxydécanoïque, l'acide 5-hydroxydécanoïque, et l'acide 4-hydroxy-2, 2-diphénylbutanoïque, comme forme acide libre ou sel.

14. Utilisation de la composition de l'une quelconque des revendications 1 à 13, dans laquelle l'agent dermatologique topique est sélectionné dans le groupe constitué par l'hydroquinone et le monoéther d'hydroquinone, notamment l'éther de monométhyle et de monobenzyle.

15. Utilisation de la composition de la revendication 14, dans laquelle lesdits acides hydroxycarboxyliques et l'acide associé cétocarboxylique, et ses formes ester, lactone ou sel, comportent l'acide glycolique, l'acide benzilique, l'acide tropique, l'acide lactique, l'acide malique, l'acide citrique, l'acide isocitrique, l'acide citramalique, l'acide tartronique, l'acide tartari-

que, l'acide gluconique, l'acide galactonique, l'acide alpha hydroxyisobutyrique, l'acide phényllactique, l'acide mandélique, l'acide atrolactique, la gluconolactone, la galactonolactone, l'acide ribonique, la ribonolactone, l'acide pantoïque, la pantolactone, l'acide pantothénique, l'acide alpha hydroxybutyrique, l'acide beta hydroxybutyrique, l'acide quinique, l'acide pyruvique, l'acide phényle pyruvique,le pyruvate de méthyle, le pyruvate d'éthyle, l'acide ascorbique, l'acide benzoyle formique, le formate de méthyle benzoyle et le formate d'éthyle benzoyle.

16. Utilisation de la composition de l'une quelconque des revendications 1 à 13, dans laquelle l'agent dermatologique topique est un agent anti-nycotique .

17. Utilisation de la composition de l'une quelconque des revendications 1 à 4, dans laquelle ledit acide hydroxycarboxylique est l'acide glycolique.

18. Utilisation de la composition de l'une quelconque des revendications 1 à 4, dans laquelle ledit acide hydroxycarboxylique est l'acide lactique.

19. Utilisation de la composition de la revendication 10, dans laquelle ledit acide hydroxycarboxylique est l'acide citrique.

20. Utilisation de la composition de la revendication 13, dans laquelle ledit acide hydroxycarboxylique est de la gluconolactone.

21. Utilisation de la composition de la revendication 7, dans laquelle ledit acide hydroxycarboxylique est l'acide tartarique.